

Cobalt cardiotoxicity - effects on the contractile and non-contractile cells of the heart

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Exposure to cobalt is known to cause cardiotoxicity and a common source of cobalt exposure is from metal-on-metal bearings used in prosthetic joint replacements. Acute and chronic effects of cobalt at a cellular level in the heart are not well understood. This study investigated the effects of cobalt (CoCl₂) treatment on contractile and non-contractile cells of the heart. We have used isolated adult rat ventricular papillary muscles to investigate the effects of CoCl₂ on basal and isoprenaline-stimulated contractile responses. In addition, we used freshly isolated primary adult rat ventricular fibroblasts maintained in short-term culture to assess the effects of CoCl₂ on cell viability and proliferation. Stimulation of isolated ventricular papillary muscles with the positive inotrope isoprenaline (1 μ M) resulted in a consistent increase (~35% increase) over the basal contractile response as expected. Following treatment with CoCl₂ (1 μ M) for 4h, there was a dramatic reduction in both the basal and isoprenaline-stimulated contractile responses (both~40% reduction). This effect was not due to a time-dependent decrease in contractility since in separate parallel control preparations consistent increases in contraction were observed following 1 μ M isoprenaline challenges at time zero and after 4h without CoCl₂. Examination of the effects of CoCl₂ on cardiac fibroblast proliferation and viability was performed using a range of assays. To assess effects on proliferation, MTT, neutral red and crystal violet assays were all used to compare effects of increasing concentrations of CoCl₂ on the Swiss 3T3 fibroblast cell line and primary cardiac fibroblasts. Over 72h, increasing CoCl₂ concentrations (up to 500 μ M) resulted in decreased proliferation. The MTT and Crystal violet assays showed the most reproducible results with IC₅₀ values for CoCl₂ in the range of ~300 μ M. Interestingly, further experiments using BrdU incorporation to assess proliferation suggested that cardiac fibroblasts were more sensitive to CoCl₂ treatment than Swiss 3T3s. In the former, after either 48h or 72h there was ~80% reduction in proliferation with 25 μ M CoCl₂ and almost no proliferation following 100–150 μ M CoCl₂. Cell viability in increasing concentrations of CoCl₂ (up to 500 μ M) was assessed using CFDA and propidium iodide staining. The ratio of live:dead cells decreased dramatically with increasing CoCl₂. Phalloidin-FITC was also used to examine cell viability and structure following treatment. With increasing CoCl₂ there was evidence for increased disruption of actin filaments. In conclusion, short-term low dose CoCl₂ treatment of ventricular preparations results in compromised contractile function. Treatment of non-contractile cardiac fibroblasts with higher concentrations results in decreased ability of cells to proliferate as well as long-term cell damage and death. It is likely that the cardiotoxic effects of CoCl₂ are manifest in both contractile and non-contractile cells of the heart. The underlying cellular mechanisms involved have yet to be established.